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PATENT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

#12

In re U.S. Patent No.	4,406,906
Patentees:	Horst Meyer et al
Issue Date:	September 27, 1983
Title:	CEREBRAL THERAPEUTIC AGENT AND ITS USE

Box Pat. Ext.
Commissioner of Patents
and Trademarks
Washington, DC 20231

Dear Sir:

Bayer A.G., owner of the above-identified patent, hereby grants to Louis E. Davidson, Reg. No. 18,276, complete power of attorney to prosecute the application for extension of the term of the above-identified patent, to transact all business in the Patent and Trademark Office connected therewith, and to receive any certificate of extension of the patent term.

Respectfully submitted,

BAYER A.G.

By [signature]

Title Country Secretary

Date ~~Feb 17, 1989~~ Feb 17, 1989

Miles Inc.
P.O.Box 40
Elkhart, IN 46515

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Louis E. DAVIDSON

(Typed or Printed Name of Person Mailing Paper or Fee)

Louis E Davidson

(Signature of Person Mailing Paper or Fee)

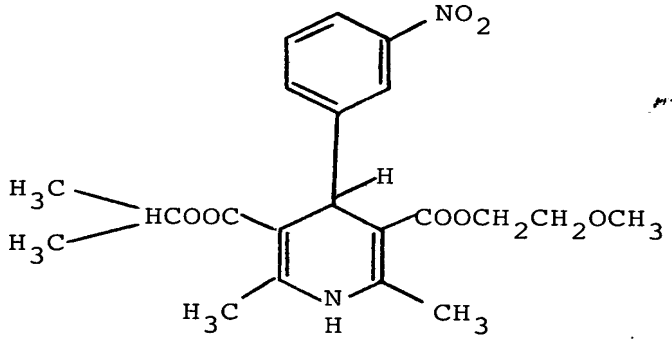
Box Pat. Ext.
Commissioner of Patents
and Trademarks
Washington, DC 20231

Dear Sir:

This is an application on behalf of the patent owner Bayer A.G. (Applicant) for extension of the term of the above-identified patent under the provisions of 35 U.S.C. 156.

This application relates to nimodipine (NIMOTOP ®) whose chemical name is 1,4-dihydro-2,6-dimethyl-4-(3'-nitrophenyl)-pyridino-3-(β-methoxyethyl ester)-5-isopropyl ester. It is also known as isopropyl-(2-methoxyethyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,-5-pyridine-dicarboxylate.

It has the structural formula:



It also has a molecular weight of 418.5 and a molecular formula of $C_{21}H_{26}N_2O_7$.

Nimodipine is a yellow crystalline substance, practically insoluble in water. In its approved form it is contained in soft gelatin capsules for oral administration. Each liquid filled capsule contains 30 mg. of nimodipine in a vehicle of glycerin, peppermint oil, purified water and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, titanium dioxide, and purified water.

This product was subject to regulatory review under Section 505(b) of the Federal Food, Drug, and Cosmetic Act.

This product received permission for commercial marketing or use under the above Act on December 28, 1988.

The only active ingredient in this product is nimodipine, and it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

This application is being submitted within the sixty day period permitted for submission pursuant to 37 CFR 1.720 (f). The last day on which this application could be submitted is February 25, 1989 (extended by 37 CFR 1.7 to February 27, 1989).

Extension is being sought for U.S. Patent No. 4,406,906. The inventors are Horst Meyer, Friedrick Bossert, Stanislav Kazda, Friedrick Hoffmeister and Wulf Vater. It issued on September 27, 1983 and its date of expiration is September 27, 2000.

Enclosed is a copy of U.S. Patent No. 4,406,906 along with a copy of the maintenance fee receipt. There was no disclaimer, certificate of correction or reexamination certificate issued for this patent.

U.S. Patent No. 4,406,906

This U.S. Patent No. 4,406,906 claims the approved method of using the approved product.

The approved method of using nimodipine is for the improvement of neurological outcome in patients following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms.

Nimodipine is defined in the approved product as isopropyl-(2-methoxyethyl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylate. Another way of naming this compound is 1,4-dihydro-2,6-dimethyl-4-(3'-nitrophenyl)-pyridino-3-(β-methoxyethyl ester)-5-isopropyl ester.

The approved dosage form is a medicament capsule to be administered orally.

Claim 1 of the above patent reads:

A method of combating pathologically reduced cerebral functions and performance weaknesses, cerebral insufficiency and disorders in cerebral circulation and metabolism in warm-blooded animals which comprises administering to the said animals a cerebral specific effective amount for treating said conditions of 1,4-dihydro-2,6-dimethyl-4-(3'-nitrophenyl)-pyridino-3-(β-methoxyethyl ester)-5-isopropyl ester either alone or in admixture with a diluent or in the form of a medicament.

Claim 4 of the above patent reads:

A method according to Claim 1 or 2 in which the active compound is administered orally.

The approved nimodipine compound has the same name and is the active material specifically set forth in Claim 1. The approved method of using this compound is a method of combating disorders in cerebral circulation in humans (warm-blooded

animals). Thus Claim 1 reads on the approved method of using the approved product, and Claim 4 reads on the approved oral administration method for the approved product.

U.S. Patent No. 4,406,906

The effective date of the IND application was June 29, 1979 and the IND number was 16,524.

The date on which the NDA was initially submitted was September 16, 1982 and the NDA number was 18-869.

The NDA was approved on December 28, 1988.

U.S. Patent No. 4,406,906

The initial marketing applicant was Delbay Laboratories, a licensee of the Applicant. At the time of the submission of IND 16,524 on June 29, 1979, Delbay submitted Protocol No. D78-003 and information as to clinical studies to be performed under such protocol.

On November 27, 1979, Delbay submitted to the FDA amendments relating to four studies being conducted under Protocol No. D78-003.

On June 29, 1981, Miles Laboratories, Inc. a licensee of Applicant, assumed responsibility for IND 16,524 and became the marketing applicant, and on August 5, 1981, Miles notified the FDA that it had assumed responsibility for this IND.

On November 9, 1981, Miles submitted to the FDA an amendment to Protocol No. D78-003 along with a case report on studies being conducted since June, 1979.

On September 16, 1982, Miles submitted an NDA containing all the information about the nimodipine product and clinical study reports up to that time. The FDA notified Miles on October 1, 1982 that the NDA was received and assigned No. 18-869.

On November 29, 1982, Miles submitted case report forms for five studies under Protocol No. D78-003 as requested by the FDA.

On December 13, 1982, Miles submitted bioavailability data to the FDA.

On February 2, 1983, Miles was notified by the FDA that DMF 4767 had been assigned to R.P. Scherer to manufacture nimodipine capsules for Miles.

From March 14, 1983 to April 15, 1983, there were discussions between Miles and the FDA concerning withdrawal of the NDA

without prejudice to collect clinical data on an increased dosage level.

On April 19, 1983, Miles withdrew the nimodipine NDA without prejudice. The FDA assigned to this NDA a review Drug Classification of 1A.

On May 19, 1983, FDA acknowledged withdrawal of the NDA and requested additional information on biopharmaceutics, chemistry, in-process tests for nimodipine solution, stability, reference standard, bulk drug substance, disintegration/dissolution rate testing and the R.P.Scherer operation (DMF4767).

On November 11, 1983, Miles submitted to the FDA information requested in the letter of May 19, 1983.

From December 1983 to August 1984 information was being collected and discussions were held with the FDA about resubmitting the NDA.

On August 13, 1984, Miles resubmitted the NDA.

On October 31, 1984, Miles submitted extended summaries of pharmacology, pharmacokinetics and toxicology requested by the FDA.

From November 1984 to March 1985, Miles had various discussions and correspondence with the FDA about the NDA.

On March 15, 1985, FDA notified Miles that the NDA was considered withdrawn and resubmitted on March 6, 1985.

From August 1985 to January 1986, there were several discussions and correspondence between Miles and the FDA concerning information for the NDA and its status.

On March 28, 1986, the Cardiovascular Advisory Committee of the FDA reviewed the nimodipine data and requested that the NDA be withdrawn and resubmitted with specific additional information on clinical studies using nimodipine for subarachnoid hemorrhage.

From April 1986 to July 1986, there was activity to collect the information requested by the FDA.

On July 9, 1986, Miles submitted the requested information and the FDA indicated that the NDA review would be reactivated.

From July 1986 to December 1988 there were many separate discussions and correspondence between Miles and the FDA concerning the status of the NDA.

On December 28, 1988, the NDA was approved by the FDA. Such approval was granted to Miles Inc. (formerly Miles Laboratories, Inc.).

U.S. Patent No. 4,406,906

It is the opinion of the Applicant that this patent is eligible for an extension. This extension should be for two (2) years which is the maximum extension allowable under 35 USC 156 (g) (4) (C). The eligibility for this extension is calculated as follows:

A. The IND was filed on June 29, 1979, and there was due diligence toward filing the NDA initially on September 16, 1982. The regulatory review period under 35 USC 156 (g) (1) (B) (i) was thus the 1174 days (3 years, 2 months, 17 days) between these two dates. Under 35 USC 156 (c) (2) only one-half of this time or 587 days (1 year and 7 months) are eligible for extension.

B. There was due diligence between the initial filing of the NDA on September 16, 1982 and the approval of the NDA on December 28, 1988. The regulatory review period under 35 USC 156 (g) (1) (B) (ii) was thus 6 years, 3 months and 12 days.

This total regulatory review period under 35 USC 156 (g) (1) (B) of at least 7 years and 10 months provides adequate eligibility for the 2 years maximum extension allowed.

At the time the NDA was approved, the period remaining in the term of the above patent was 11 years, 8 months and 30 days. Therefore, an extension of 2 years provides a total period of remaining patent life plus extension of 13 years, 8 months and 30 days which is less than the maximum of 14 years allowable under 35 USC 156 (c) (3).

U.S. Patent No.4,406,906

The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Enclosed is a check for the $550 fee for receiving and acting upon this application for extension.

All inquiries and correspondence relating to this application for patent term extension are to be directed to:

Louis E. Davidson
Miles Inc.
P.O. Box 40
Elkhart, IN 46515
Telephone: 219-264-8393

Enclosed herewith is a certified copy of this application.

I, the below-designated official of Bayer A.G., who is authorized to obligate Bayer A.G., hereby declare that:

1. I have reviewed the preceding pages of this application for extension of the term of U.S. Patent No. 4,406,906 and understand the contents thereof;

2. I believe the patent is subject to extension pursuant to 37 CFR 1.710;

3. I believe an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

4. I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

We also hereby declare that all statements made herein of ~~my~~ our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent for which such extension is sought.

Respectfully submitted,

BAYER A.G.

By [signature] [signature]

Title Secretary Secretary

Date Feb. 17, 1989 Feb 17, 1989

Miles Inc.
P.O.Box 40
Elkhart, IN 46515

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